Integrated Medical Model -- Renal Stone Module

Completed Technology Project (2011 - 2015)

Project Introduction

The Exploration Medical Capability Element of the Human Research Program carries the risk of not being able to treat ill or injured crewmembers. Gap 4.13 in the Exploration Medical Capability Research Plan is the "Lack of lithotripsy or other capability to treat a renal stone." The description of this gap states that, "Given the high probability of kidney stone formation in crew members during long duration missions the capability to perform Lithotripsy is highly desirable."

During all spaceflight missions to date, renal stone incidence is actually lower than what would be expected in the general population or in the analog population utilized by the Lifetime Surveillance of Astronaut Health (LSAH). After astronauts return to Earth, however, the incidence rate increases and surpasses both the rate of the general population and the LSAH analog population, with the astronaut incidence rate of calcium oxalate stones approximately doubling that of the general US population. If these trends persist with the reintroduction of even fractional gravity, renal stones during a Mars mission could become a serious problem, not only in terms of astronaut health, but also in terms of the resources required to adequately treat the condition. A Bayesian update analysis of the data above suggested an approximately 5% probability of at least one crewmember developing a renal stone during a Mars mission.

Given the nature of these data, the Glenn Research Center (GRC) Integrated Medical Model (IMM) team developed a proof of concept probabilistic simulation of renal stone formation during a long duration exploration mission. While somewhat limited in scope, this simulation included both probabilistic and deterministic components. The deterministic components were developed to support the probabilistic analysis. Key findings from this work included:

1) As the stone grows larger, the governing equation says the rate of growth will increase, which is why the probabilistic analysis picks up the seed size as being influential.

2) The probabilistic model demonstrates identical sensitivity for Calcium and Oxalate, suggesting that a more detailed surface chemistry simulation needs to be conducted.

3) The sensitivities for the dwell time of a stone show pronounced differences between the 2.0 L/day and 2.5 L/day cases resulting in a 68.6% change in the probability of one stone reaching the effective diameter of a nephron from heterogeneous growth only. This result has a standard deviation of 0.237.

As part of the validation process for this module, the task underwent a subject matter expert review of the work done to date. The review was favorable with indication that an increase model fidelity was required, as outlined in Steps 1-3 below.

1. Determine expected incidence rate of renal stones during exploration

Integrated Medical Model -- Renal Stone Module

Table of Contents

missions and how this rate is affected by new countermeasure activities.

2. Provide a probabilistic simulation that allows the Exploration Medical Capabilities Element of the Human Research Program to develop medical kits appropriate to the level of risk of renal stone formation.

3. Provide a probabilistic simulation that allows the Exploration Medical Capabilities Element of the Human Research Program the ability to quantitatively evaluate the effect of different operations scenarios on the ability of a given medical kit to adequately treat an ill or injured crew member.

The GRC IMM task team is currently working to extend the capabilities of the deterministic model used as the parameter integration function to include both promoters, inhibitors, agglomeration, wall interaction effects, and gravity components. Once this is matured, it will be wrapped with a probabilistic simulation representing the scenarios and physiological parameter variation typical of spaceflight to assess the likelihood of renal stone formation.

Once completed, The Renal Stone Formation Simulation Module (RSFSM) will provide a state-of-the-art computational capability that can not only be used to more directly investigate the renal stone size distributions and the statistical propensities for developing a critical stone incident for future mission scenarios but also help to devise and evaluate different systematic chemical or physical intervention countermeasures for preventing their occurrence in future.

Anticipated Benefits

Nephrolithiasis constitutes as one of the most common diseases that has afflicted man for centuries. Indeed, one of the first evidences of renal stones in humans was found in an Egyptian mummy at El- Amrah dating back to 4800 B.C. Today, approximately 5% of the U.S. population develops clinically significant urinary calculi in their lifetime. However, renal stone disease is not only a concern on Earth, but could conceivably pose as a serious risk to the astronauts' health and safety in space. The physiological, environmental, and dietary conditions imposed by space travel and weightlessness can easily increase this risk as a recent survey of renal stone formation in U.S. astronauts has revealed 14 recorded episodes. Russian medical science investigators have also noted multiple stone events among the Soviet cosmonauts. The most serious one was an in-flight renal stone occurrence that nearly caused the the Russian mission to be aborted.

The Renal Stone Formation Simulation Module (RSFSM) developed as part of this task is designed to inform NASA's Integrated Medical Model (IMM) with the likelihood and associated uncertainty of astronauts developing kidney stones upon long-term exposure to microgravity, as well as upon re-entry to a

Organizational Responsibility

Responsible Mission Directorate:

Space Operations Mission Directorate (SOMD)

Lead Center / Facility:

Johnson Space Center (JSC)

Responsible Program:

Human Spaceflight Capabilities

Project Management

Program Director:

David K Baumann

Project Manager:

Erik L Antonsen

Principal Investigator:

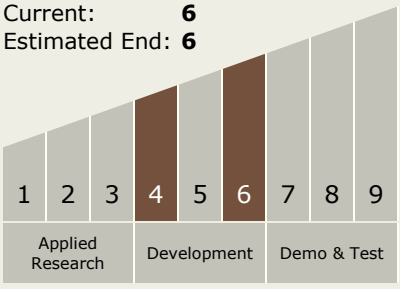
Mohammad Kassemi

Co-Investigator:

Jerry G Myers

Technology Maturity (TRL)

Start: **4**
Current: **6**
Estimated End: **6**



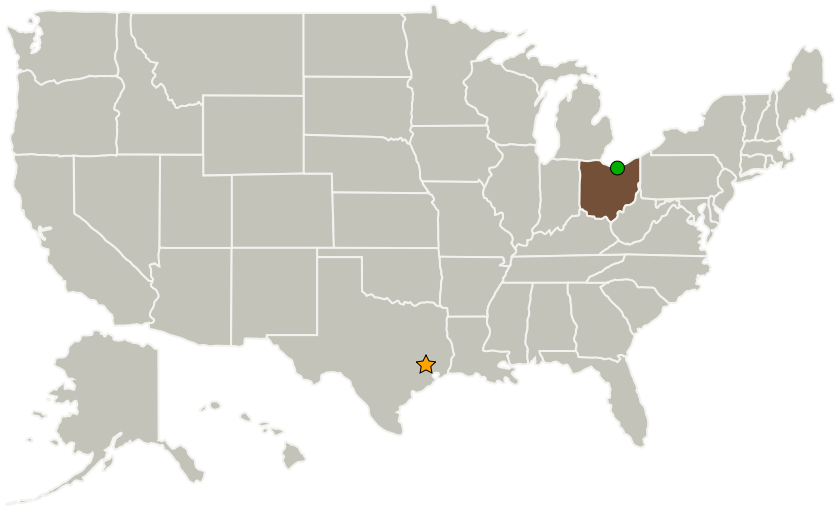
Integrated Medical Model -- Renal Stone Module

Completed Technology Project (2011 - 2015)

gravitational field. The computational module will be able to assess the effects of various design reference mission scenarios, thus allowing mission planners, medical kit designers, and clinicians to compare the efficacy of various countermeasures devised to reduce the probability of developing renal stone incident during the mission. The understanding that these simulations provide will also help to improve the astronauts' screening protocols.

The benefits of developing this computational capability is not limited to space applications but will extend back to impact clinical and scientific medicine on Earth. As a state-of-the-art research tool and virtual hypothesis-tester, RSFSM will expand the current level of understanding of renal stone disease. It will also serve as a tool to help improve clinical procedures for screening and treating nephrolithiasis on Earth and devise physical and/or pharmaceutical interventions to help the nearly 15 million Americans who currently suffer from this ailment today.

Primary U.S. Work Locations and Key Partners



Technology Areas

Primary:

- TX06 Human Health, Life Support, and Habitation Systems
  - TX06.3 Human Health and Performance
    - TX06.3.1 Medical Diagnosis and Prognosis

Target Destinations

The Moon, Mars

Integrated Medical Model -- Renal Stone Module

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Organizations Performing Work	Role	Type	Location
Johnson Space Center(JSC)	Lead Organization	NASA Center	Houston, Texas
Glenn Research Center(GRC)	Supporting Organization	NASA Center	Cleveland, Ohio
National Center for Space Exploration Research(NCSER)	Supporting Organization	US Government	

Primary U.S. Work Locations
Ohio

Project Transitions

January 2011: Project Start

Integrated Medical Model -- Renal Stone Module

Completed Technology Project (2011 - 2015)

December 2015: Closed out

Closeout Summary: In this work analytical Population Balance Equation (PBE) and Computational Fluid Dynamics (CFD) m odels were developed to predict the steady state size distribution of nucleating, growing, and agglomerating calcium oxalat e (CaOx) renal calculi during their transit through the kidney in 1g and microgravity based solely on the renal biochemical p rofile of the subject as input. The PBE model was verified through comparison with the published results provided by severa l MSRPP crystallization experiments including an in-vitro calcium oxalate experiment related to renal stone formation with e xcellent agreements. For the PBE renal stone formation simulation studies, four subjects were considered based on their pu blished 1g and microgravity biochemical profiles, namely -- 1g normal, microgravity astronaut, and 1g recurrent and micro gravity stone-formers. Parametric simulations were performed to assess the impact of alterations in renal biochemistry of t he astronauts due to microgravity exposure on the risk of critical CaOx renal stone formation during long duration missions and to quantify the efficacy of using citrate and pyrophosphate dietary supplements and increased hydration as possible co untermeasures for reducing this risk. Through comprehensive numerical case studies performed by the PBE model the follo wing assessments were made: 1. The PBE model was successful in clearly distinguishing between a 1g normal and a 1g rec urrent stone-former based on their published 24 hr urine biochemical profiles. 2. The predicted CaOx crystal aggregate size distribution for a microgravity astronaut were closer to those of a recurrent stone-former on Earth than a normal risk free s ubject in 1g underscoring the detrimental effect of space altered renal biochemistries. 3. Due to microgravity renal biochem ical alterations, the increase in risk level for developing renal stone in microgravity was relatively more significant for a nor mal person going to space than a stone former. However, numerical predictions also clearly underscore that the stone-form er subject has still by far the highest absolute risk of critical stone formation during space travel. 4. For stone-formers both on Earth and in Space depletion of calcium and oxalate is an important factor to be considered. This points to the shortcomi ng of the relative supersaturation levels determined by the 24 hr urine measurements performed distal to the growth proce ss as a definitive measure of the risk. 5. Agglomeration was found to be a crucial mechanism for stone size enhancement b oth in 1g and microgravity. 6. Citrate was found to be an effective inhibitor of both growth and agglomeration. Our numeric al predictions indicate that urine, due to its normal citrate content, is already, to a large extent, inhibited against growth an d agglomeration of CaOx crystals. Any additional increase in citrate beyond its average normal urinary levels on Earth throu gh dietary supplements is beneficial but only to a limited extent. However, the model also predicts that any decline in the ci trate levels during space travel below its normal urinary values on Earth could easily move the microgravity astronaut subje ct into the stone-forming risk category. So the current results strongly recommend for use of citrate as a dietary counterme asure to prevent the adverse effect of any space-induced hypocitraturia during the future missions. 7. Pyrophosphate was a lso found to be an effective direct inhibitor of growth. Results indicate that minimal pyrophosphate concentrations in urine c an move the maximum CaOx aggregate size predicted for the microgravity astronaut from a near critical value of 140 micro ns to a definitively safe range below 10 microns. These promising predictions suggest that more comprehensive experiment al assessment of use of pyrophosphate and other similar inhibitors such as phytic acid, and osteopontin as dietary counter measures for the space program are warranted. 8. Hydration can act as an effective promoter or inhibitor of renal stone de velopment in 1g and microgravity. Our results indicate that dehydration during space travel that may cause astronaut urina ry volumes below 1.5 liters/day can easily move a preflight non-stone-former to the population densities and renal stone siz e ranges resembling the 1-g recurrent stone formers. Augmented hydration levels that produce up to 3 liters/day urinary o utput were also simulated and numerical results indicate that urinary volumes from 2.5 - 3 liters/day can serve as an excell ent and effective countermeasure. Thus based on our results, a ½ liter increase in urine output from the current guideline l evel of 2.0 liters/day to 2.5 liters/day is recommended because it is predicted that it will provide considerable inhibitive ben efits, moving the astronaut well into a risk free range. In this work, we only investigated the effect of variation in the direct inhibitive action by citrate and pyrophosphate. For the citrate case there is also an indirect inhibition due to speciation. This contribution was included in our model only at a fixed level representative of a standard urine biochemistry. In order to con sider the impact of indirect inhibition as a function of citrate concentration, the use of speciation codes such as JESS or Equi l2 is required to account for the bounding of calcium ions with citrate in forming soluble complexes that lowers the supersat uration levels of CaOx. Coupling of JESS computations with the current PBE renal stone model will be undertaken as part of our ongoing work in this area with the goal of providing a more comprehensive assessment of both direct and indirect inhibi tion potentials of the citrate and hydration countermeasures in near future. There are two main factors that will determine whether a critical stone incident will occur or not. First is the renal biochemistry that dictates the rate of stone size enhance ment due to growth and agglomeration and the second is the residence time of renal calculi that is determined by their tran sport through the nephron by the urinary flow. The lag that might occur due to nonslip boundary condition (in both 1g and microgravity) or due to gravity effects in upward flowing tubules (only in 1g) or due to nucleation and growth on Randall pl aque surfaces or on injured sections of the nephron could not be included in the present "lumped" PBE transport analysis. I

Stories

Abstracts for Journals and Proceedings
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Project Website:

https://taskbook.nasaprs.com